General Concepts of Neoplasia

Cancer Growth

Following the stem-cell theory of cancer, it only takes **one cell** to spawn the entire cancer. One cell develops sufficient mutations to become malignant. That one cell then acts as a **stem cell**. Stem cells **divide slowly** and exist in **small numbers** within a tumor. Stem cell division is by **asymmetric mitosis**, resulting in a **progenitor cell** and the original **stem cell**. The progenitor cells are not fully differentiated cells (otherwise they wouldn't be malignant). Subsequent progenitor divisions are **symmetric** and **divide rapidly**, so have a high turnover. This means the progenitors make up the bulk of a tumor.

Cancer cells ignore cell cycle regulation, and so **proliferate continuously**. One progenitor becomes two, two become four, four become eight—each division causes a doubling of the population of cancer cells. A **doubling time** is determined by the time spent in **G_0/G_1** because S, G_2, and M have a **fixed duration**. A tumor will be **noticeable** (will have clinical symptoms) at **10^9 cells**, which takes **30 doublings**. A tumor will become **incompatible with life** at **10^{29} cells** or **100 doublings**. The more mitotically active, the shorter G_1, the faster the doubling time and the more vulnerable to chemo the tumor is. The **doubling rate** is the **theoretical time** it would take cancer cells to double in number if all cells were dividing AND **if there were no other influences**. The doubling rate, the term, is not influenced by growth fraction or cell death rate. Because not all cells are dividing, and some cells may be dying, the actual time it takes for a tumor to double in size is **longer than its theoretical time** defined as **doubling rate**.

The **growth fraction** is the percentage of cells with sufficient nutrients to continue to divide. While there may be no regulation of cell divisions and no regulation on how frequently the cell can divide, all cells need the prerequisites for copying—cytoplasm, amino acids, sugar, oxygen, lipids. So while theoretically all cells in a tumor are doubling constantly, the number is usually less than that. Doubling suffers increasingly diminished efficiency the bigger the tumor gets. Cells get deprived of the basic materials of copying, and so **not all cells in a cancer are dividing**. Small cancers with easy access to nutrients are closer to true doubling, while large tumors have progressively less and less division, so will take longer to double in size. The **growth fraction** refers to the cells actively proliferating. These cells will contribute to an **increase in the tumor size**—all other cells are either not dividing or are dying, so cannot contribute to growth. It also implies a **stagnation fraction** (whatever is left over from the growth fraction). These cells remain alive, but do not replicate, so do not change the total cell population in the next generation.

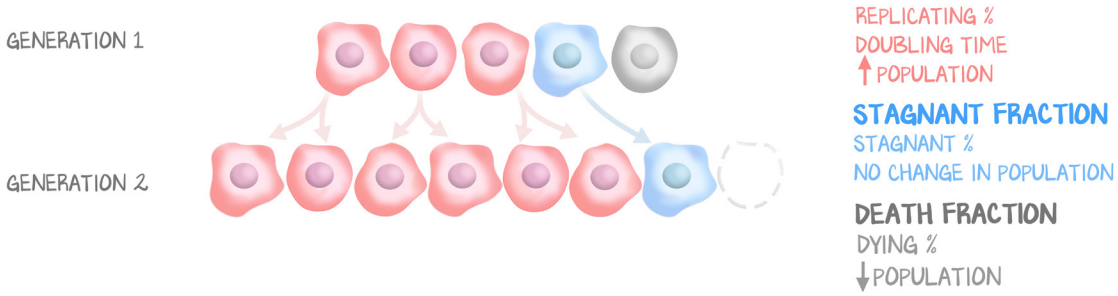

Figure 10.1: Cancer Growth
This figure illustrates the concepts of growth fraction (red), stagnation fraction (blue), and death fraction (black), and their effect on the overall tumor burden. Every tumor is a heterogeneous mix of cells actively proliferating, quietly resting, and actively dying, even before treatment is started.

Not only can cells deprived of their nutrients stop dividing, but if deprived enough, they can die. Tumors grow rapidly. Those that outgrow their vascular supply (unregulated proliferation without sufficient

angiogenesis) become necrotic—cancer cells are vulnerable to hypoxemia, too. So even before treatment with chemo, there may be a proportion of cells dying off on their own. This concept is the **cell death rate**. The cell death rate, or death fraction, **decreases the number of cells** in the next generation.

Log-Kill

Log-kill is a concept used for **cell-cycle-specific chemotherapeutic agents**. It says that with each administration of chemotherapy, a **proportion of cells** will die, not a raw number. That means cell-cycle-specific drugs kill with first-order kinetics. This almost sounds great. If chemo drugs kill cancer on a first-order kinetic curve, then the cancer would be cured after 7-10 "cancer half-lives"—only 7-10 treatments for a cure! But that's not reality. Because cancer does not sit by idly waiting for the next dose. Instead, the tumor fights back by proliferating between dose administrations.

A 3-log-kill dose of an effective drug would bring 10^{12} to 10^{9}, 10^{9} to 10^{6}, and 10^{6} to 10^{3}. The problem with this concept is threefold. One problem is that the cancer **proliferates** between doses, so to be effective, the next dose would need to be given before the cancer was able to re-attain its starting number. The second problem, which was discussed in Lesson #8: *Cell Cycle Chemotherapy*, is that chemotherapy also log-kills good cells, like bone marrow. And because they aren't malignant, they won't proliferate as quickly as tumor cells. If the marrow recovers more slowly than the tumor, failure is inevitable. Third, most of what chemo kills is the more rapidly dividing progenitor cells, not the stem cells. And it only takes one stem cell to bring back the entire lesion.

This is why we say chemotherapy puts cancer into **remission** rather than cures it. **The only way to cure cancer is early detection and surgical removal before invasion.** Chemotherapy and radiation for an advanced cancer is just a fight for time that will ultimately fail.

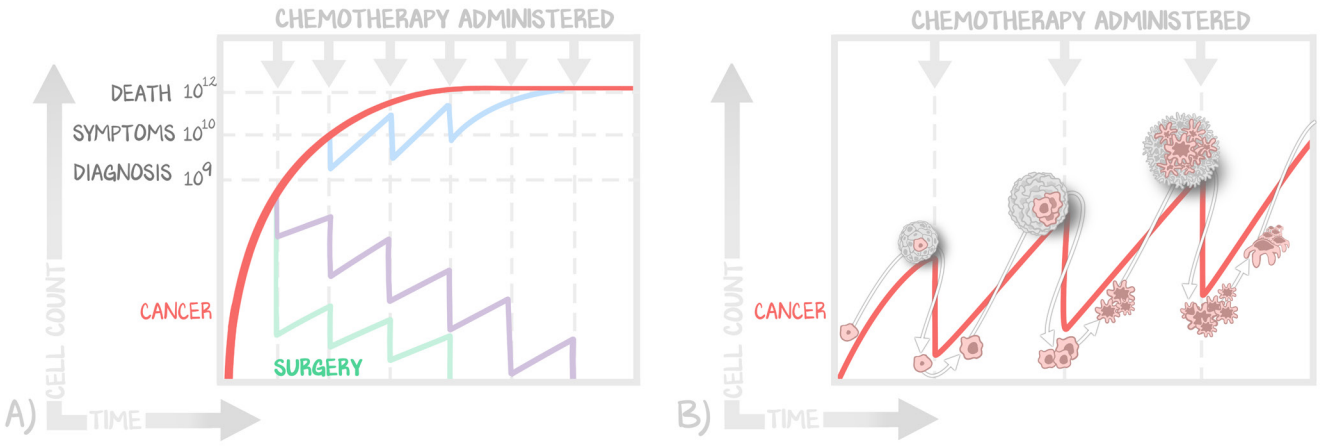

Figure 10.2: Log-Kill and Heterogeneity
(a) Log-kill means a certain proportion of cells will be killed. Since it takes to about 10^{9} cells for a tumor to become perceivable, there will be many cells ready to double even after a log-kill. Starting log-kill treatment when there are many cells will lead to failure—the remaining cells will proliferate faster than the chemotherapy can kill (dark blue trace). If started early enough, repeated treatments will eventually lead to remission (light blue trace). It is best if the bulk of the cancer cells can be removed surgically, leaving only a small number of cells, against which radiation of chemotherapy rapidly achieves remission. (b) Because those cells that are not killed by treatment continue to develop mutations, those that live become resistant to chemotherapy. Only one cancer cell need remain to proliferate to a new tumor, so we say "remission" and not "cure" unless the cancer is caught at precancer or stage I.

Worse, the cells in a tumor will demonstrate **heterogeneity**—they are breaking their DNA in different ways. When chemo comes around and kills a bunch off, the ones that survive will be better adapted to survival. Then **clonal expansion** of the survivors increases risk of **resistance**.

Neoplasia (unregulated cell growth) is **monoclonal**. And while cancer starts off monoclonal, heterogeneity implies that as cells mutate further, multiple cell lines (albeit very closely related to the stem cell) develop.

Treating Cancer

The log-kill section was sort of depressing. The good news is that the log-kill-destined-to-fail bit was if we used chemotherapy alone to treat cancer. It's important to realize early in this career that in almost all cases, metastatic disease will be fatal. Tumor burden increasing (number of mets, size of an individual tumor) despite active treatment will be fatal. **Early detection and surgical removal is the only way to cure cancer**. That was repeated on purpose. The higher the stage, the worse the prognosis. Very few cancers get cured after they leave the organ. Other than early detection and surgical removal, cancer treatment is about buying time, not about a cure.

The options for treating cancer are **surgery** (cutting the cancer out), **radiotherapy** (zapping the tumor by combining multiple beams at the focus of the cancer—individual beams are not harmful to healthy cells, but the cumulation of all beams at the cancer causes necrosis of the tumor), and **chemotherapy**. More complicated combinations and special techniques exist, but at this point in a student's training should be left to surgical oncologists.

Chemotherapy can be **adjuvant** (given **after** surgical removal) and **neoadjuvant** (given **before** surgery). Adjuvant chemo aims to kill any cancer cells that may have been missed by surgery—make sure the surgeon didn't leave any behind. Neoadjuvant chemo aims to shrink a cancer to increase the chances of successful surgery.

Radiotherapy can be used in a similar manner. Radiation therapy can be used to kill off cancer cells missed by surgery ("adjuvant radiation"), to reduce a tumor for surgery ("neoadjuvant radiation"), and even to decrease tumor burden as a palliative measure.

Surgery used for anything other than cure of a local cancer (it has not penetrated the basement membrane) is considered **debulking**. It's used to alleviate symptoms of the cancer—bowel obstruction, lymphedema—but will not be curative. Debulking surgery is also used to reduce the original tumor burden before chemo. If there are fewer tumor cells to regrow after chemo, the log-kill effect may produce remission.

This section was simply an attempt to make these words familiar. **THE TEST WILL NOT REQUIRE YOU TO DETERMINE A COMBINATION OF THERAPIES.** Do not memorize chemotherapeutic regimens for different cancers. Do not attempt to decide when to use surgery, chemo, or radiation. The takeaways here are that **metastatic cancer kills** and **early detection with surgical removal cures**.

Carcinoma Progression

The entire tumor, all of the cancer cells within a tumor, started as just one stem cell amongst many normal cells. Eventually, that stem cell and its progenitors, unregulated and unrestricted, predominate over the local healthy tissue. Carcinomas are usually in epithelium. We can assess the intensity of dysplasia, from normal to severe, with tissue invasion and finally metastasis.

Normal cells have a **polarity**. The cells at the **basement membrane** are the progenitors of normal tissue. The cells layered on top out to the edge of the epithelium are oriented to each other and to the epithelium. Basal down, apical up, oldest cells farthest out, newer cells towards the basement membrane. The basal layer of cells is defined.

Dysplastic cells start to grow with loss of **size**, **shape**, and **orientation**. Mild dysplasia is defined by only a small percentage of the epithelial layer being dysplastic, often showing changes only in the basal layer. Moderate dysplasia shows the loss of that basal layer orientation and dysplasticity in more than half of the epithelial layer's cells. Severe dysplasia, also called **carcinoma in situ**, is a **complete loss of the basal layer**, with the **entire epithelium**, basal layer to apical surface, **replaced by dysplastic cells**. No invasion of the basement membrane has occurred.

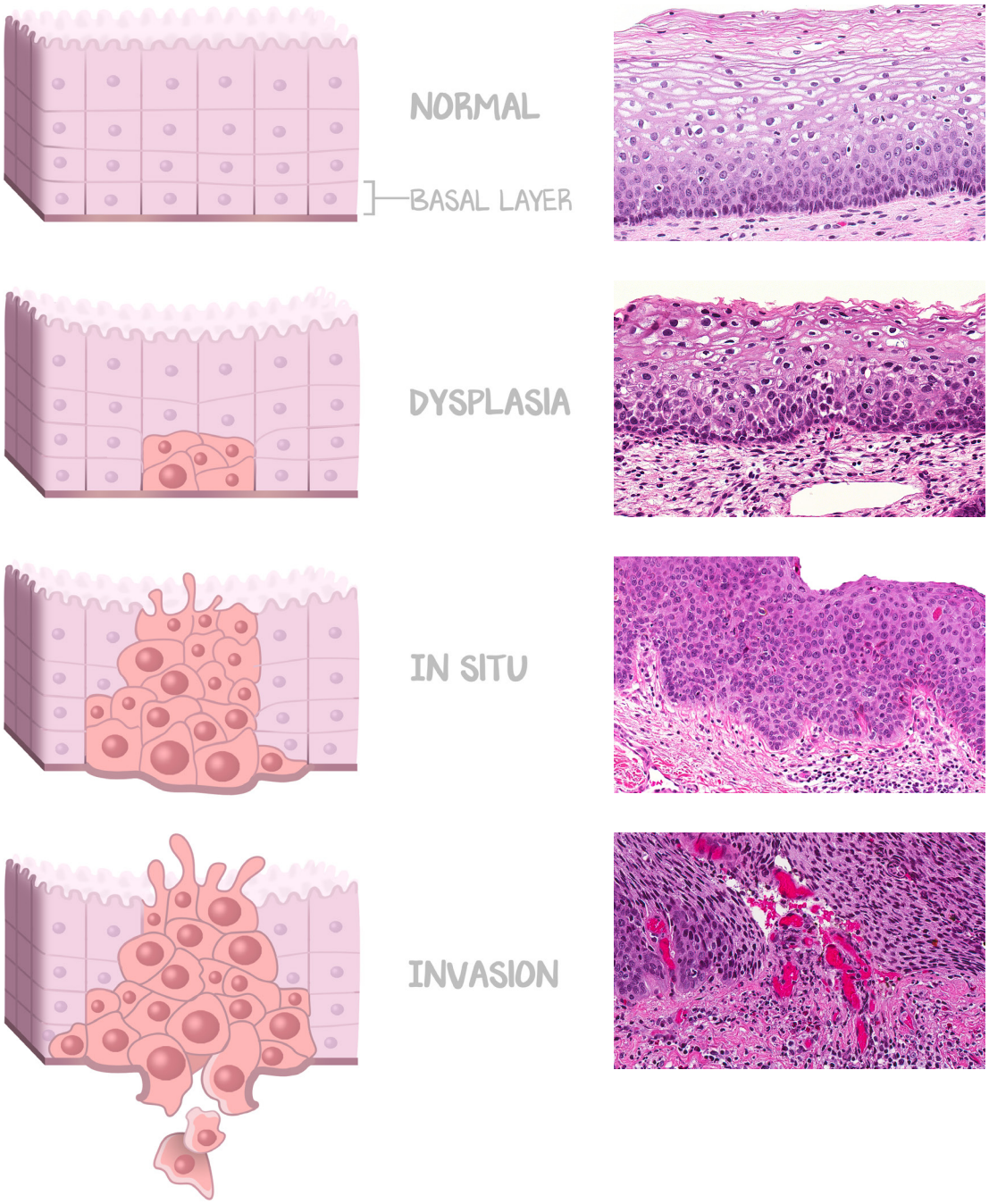

Figure 10.3: Carcinoma Progression
(a) Artist's rendition of the progression of carcinoma in an epithelial layer from normal tissue, through initial dysplasia, carcinoma in situ, and invasion of the basement membrane. (b) Histology slide of the progression of dysplasia in an epithelial layer.

Invasive carcinoma is the name for that same dysplastic tissue that manages to penetrate the basement membrane. This is **locally invasive** cancer. It has not yet metastasized. Metalloproteinases allow penetration into tissue; the loss of cadherins causes loss of cell-to-cell contacts.

Metastatic disease is the spread to distant organs by lymphatics, blood, or local spread.

Routes of Metastasis

Routes of Spread		
Lymphatic	**Hematogenous**	**Local / Seeding (Transcoelomic)**
Most carcinomas	Most sarcomas	Ovarian
	Renal cell carcinoma	Pancreatic
	Hepatocellular carcinoma	
	Follicular thyroid	
	Choriocarcinoma	

Table 10.1: Routes of Metastatic Spread
Be able to identify the route of spread of carcinomas and sarcomas, and then memorize the exceptions.

Metastasis is the **most reliable** indicator of malignancy. All malignant cancers eventually metastasize (except for brain cancer—the patient dies before it can spread). The routes are lymphatic, hematogenous, and local (also called transcoelomic).

Route 1: Lymphatics

Lymphatic spread is the route **most carcinomas** take. Exceptions are renal cell, hepatocellular, follicular thyroid, and choriocarcinoma, which spread hematogenously. Carcinomas that spread through the lymphatics first penetrate the basement membrane of their originating organ. They penetrate the underlying connective tissue and enter the lymph. The cells both actively move and are pushed by hydrostatic pressure through lymphatics. They ascend the lymphatic trunk and settle in the subcapsular sinus. Proliferation there eventually leads to penetration of the endothelium where the cancer cells invade, proliferate, and consume the node. Nodal expansion is sequential and anatomic—the node nearest the tumor is invaded first, then progressively more and more, up the lymphatic chain.

The **sentinel node** is the lymph node that should be first encountered based on the location of the cancer. For example, the **axillary nodes** are where the **outer quadrants of the breast** drain, while the **internal mammary nodes** drain the **inner quadrants** of the breast. In assessing the stage of a cancer, especially carcinomas that spread through lymphatics, the sentinel node can be very informative. If the **sentinel node is negative** for malignancy, the cancer is very likely to have been caught early enough to avoid metastasis. If the sentinel node is positive for malignancy, the cancer is malignant, and further nodes need be assessed. But just because **a lymph node is swollen** near a tumor does not mean the tumor has spread. T-cell activation within the node may simply be reactive to the cancer, which is why a sampling of the node is performed.

While not pathognomonic, certain features of lymphadenopathy make malignancy more likely versus reactive from infection. A **hard**, **firm**, **fixed**, and **nontender** lymph node suggests malignancy. A **soft**, **rubbery**, **movable**, and **tender** lymph node suggests reactive.

Route 2: Hematogenous

Hematogenous spread is the route **most sarcomas take**. As listed above, renal cell and hepatocellular carcinoma also spread hematogenously. In these cases, lymph node assessment has lower yield. These tumors grow in the parenchyma of the host organ, penetrate the basement membrane, and continue to grow into the associated vein. Despite accessing the blood stream, these tumors may not metastasize until much later. Hematogenous spread can result in **embolism** of large chunks of tumor or **thrombosis** of the associated vein. Hepatocellular carcinoma can cause **hepatic vein thrombosis**, while renal cell carcinoma can cause **renal vein thrombosis.**

Route 3: Local / Seeding

The reason why tumors such as **pancreatic cancer** and **endothelial ovarian cancer** have no screening tool, are so deadly, and kill so quickly is because **it's hard to know they are there**. In the peritoneum, full of soft organs pushed up against soft muscles without bones, these tumors can **grow asymptomatically** for quite some time before they get large enough to compress a hollow viscus or until they invade nearby organs. The peritoneum can be seeded by these tumors; **regional seeding is effectively metastasis**. Cancers that spread this way, especially in the peritoneum, usually carry a dismal prognosis for several reasons. First, diagnostic imaging may miss seeding (the surgeon who opens a patient for a Whipple procedure manually feels for peritoneal seeding before beginning, and does not perform if present). Second, by the time the tumor becomes symptomatic, it is already **advanced-stage.** Third, there are no useful screening tools for these cancers. Ovarian and pancreatic cancer are the two most common cancers to spread this way (though neither is considered a common cancer overall). Even those special populations that do get screening for ovarian cancer (high-risk patients with BRCA1 mutations, for example), get diagnosed with the malignancy at a later stage. Looking for these cancers, attempting to screen for them, is essentially futile because screening still may miss early tumors.